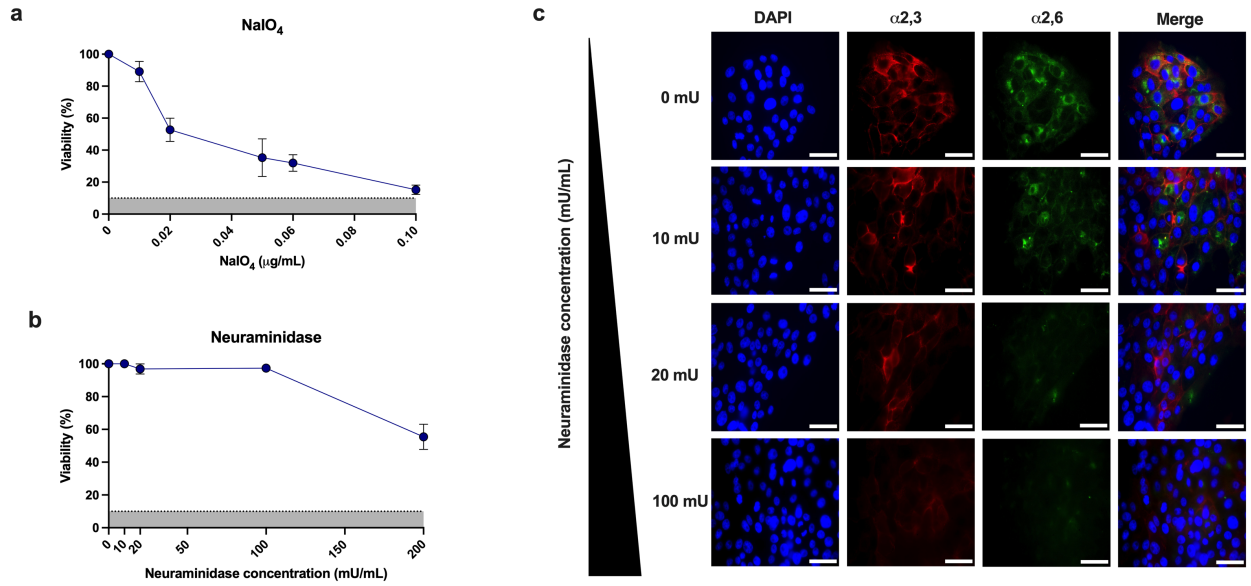
Supplementary Table 1. Primers used in this study.

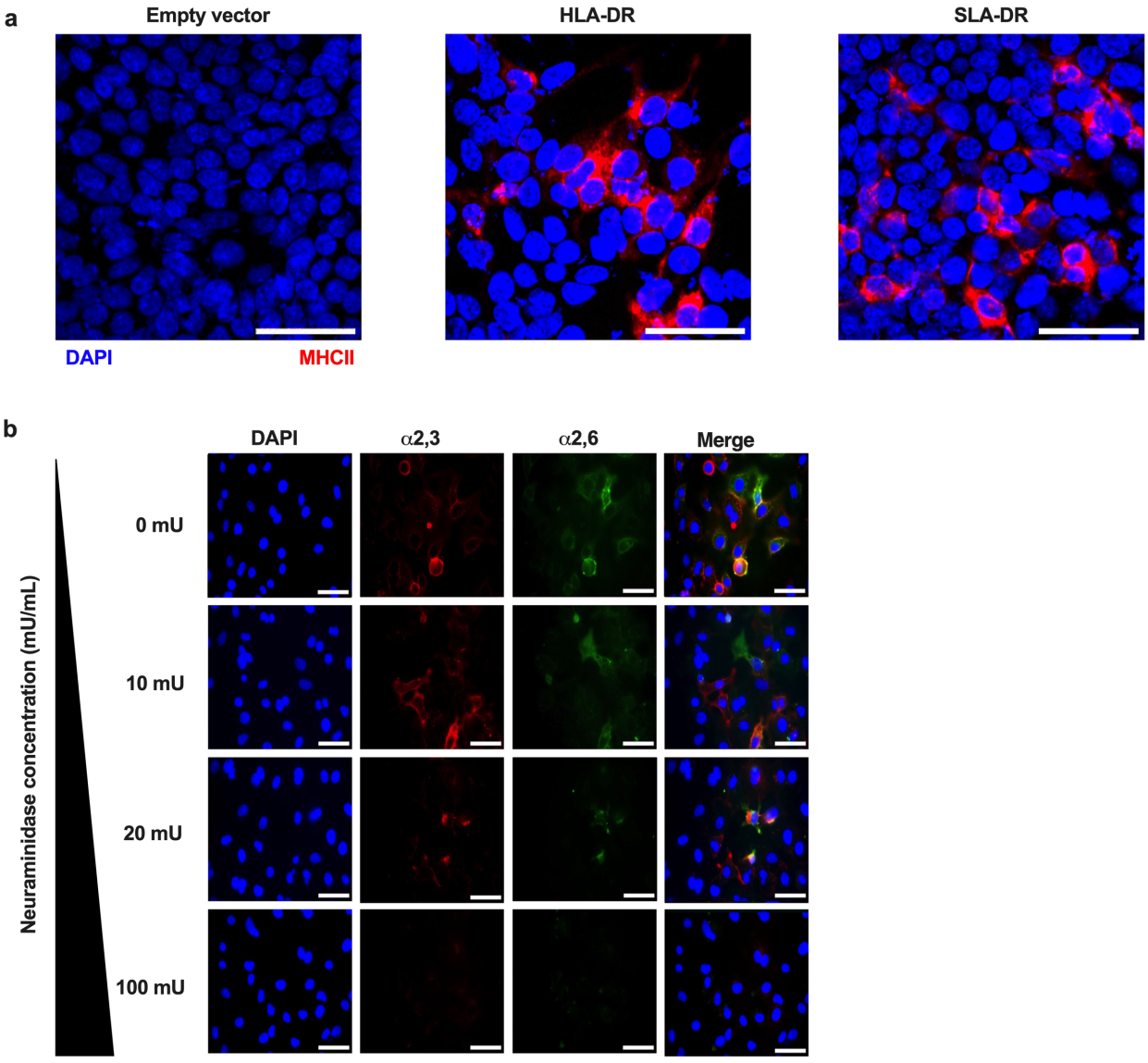
Primer		Sequence (5'-3')
HLA_DRA	F	GGAATTCCATGGCCATAAGTGG
	R	GAAGATCTTCTTACAGAGGCCC
HLA_DRB1	F	GGAATTCCATGGTGTGTCTGAAG
	R	GAAGATCTTCTCAGCTCAGGAATC
SLA_DRA	F	GGAATTCCATGACCATACTTGGG
	R	GAAGATCTTCTCACAGAGGCC
SLA_DRB1	F	GGAATTCCATGTTGCATCTGTG
	R	GAAGATCTTCTCAGCTCAGGAGG
M_titration	F	AGATGAGTCTTCTAACCGAGGTC
	R	TGCAAAGACACTTTCCAGTCTCTG
	P	GGCCCCCTCAAAGCCGA

Supplementary Fig 1. Neuraminidase treatment is not cytotoxic and efficiently removes SA form PAMs.



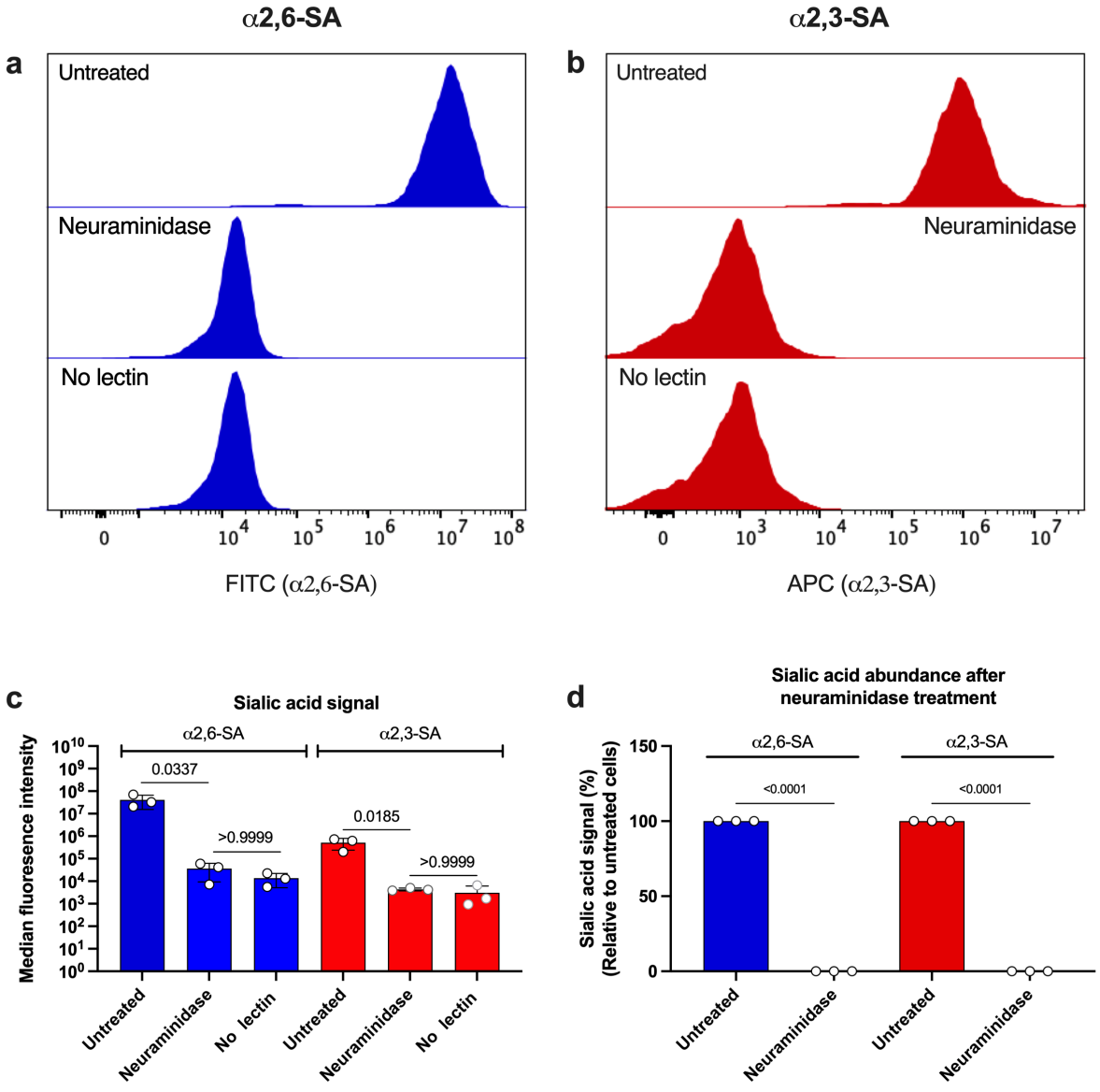
Supplementary Fig 1. Neuraminidase treatment is not cytotoxic and efficiently removes SA form PAMs. Two methods to remove sialic acid form PAMs were tested. **a,** SA oxidation with $NaIO_4$ was performed by incubating cells for with increasing $NaIO_4$ concentrations for 24 hours. After incubation, cell viability was evaluated (n=3 independent experiments). Data are presented as the mean ± SEM of three independent experiments. **b,** neuraminidase treatment of PAMs was performed for 24 hours. After treatments cell viability was evaluated for each neuraminidase concentration. Data are presented as the mean ± SEM of three independent experiments. **c,** Sialic acid on the cell surface of PAMs incubated wit 0 or 100 mU/mL of neuraminidase was evaluated by lectin staining and immunofluorescence. Scale bar represents 30 μm.

Supplementary Fig 2. Transfection of HEK-293T with MHCII-encoding plasmid yields high levels of MHCII expression.



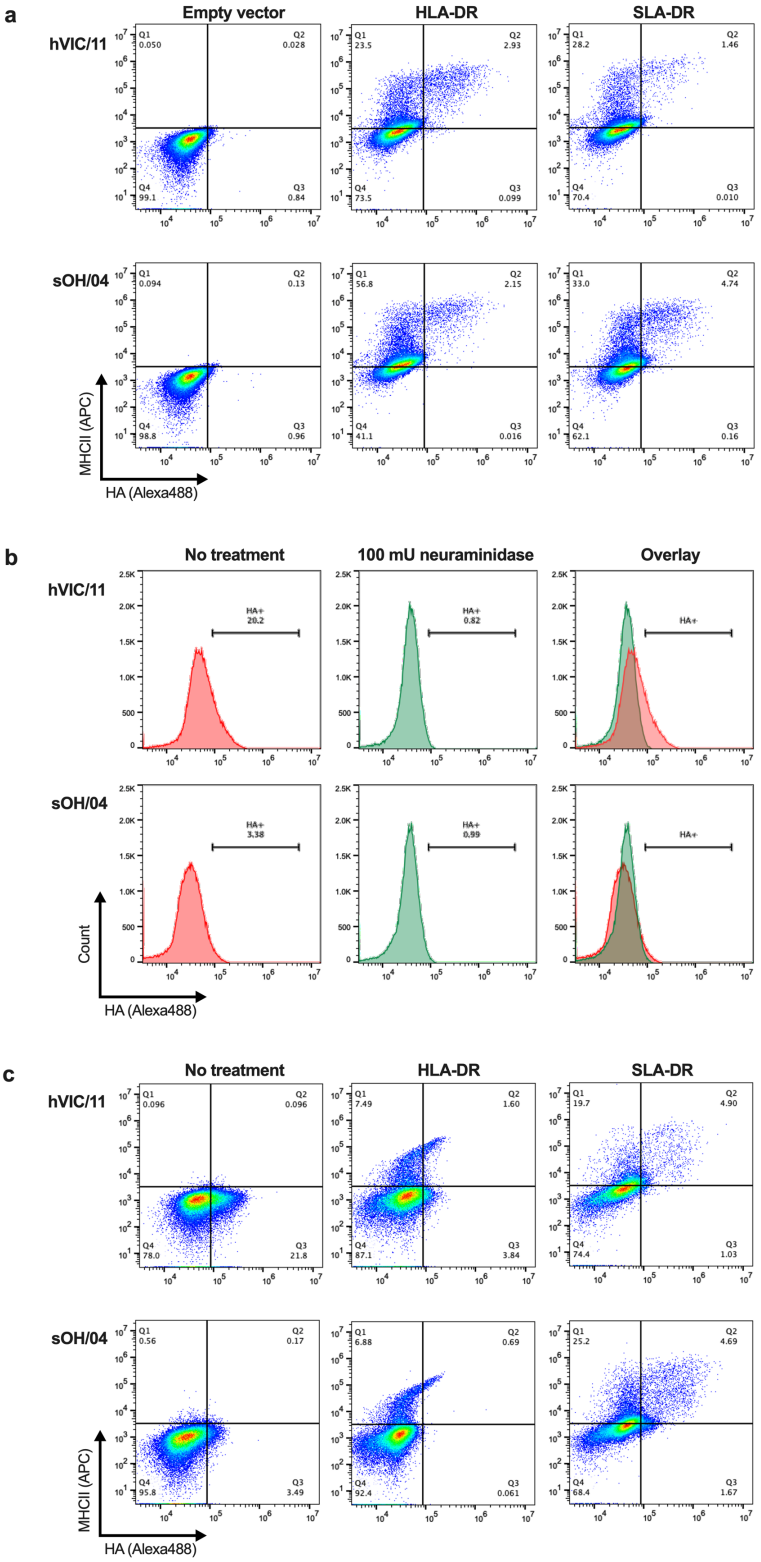
Supplementary Fig 2. Transfection of HEK-293T with MHCII-encoding plasmid yields high levels of MHCII expression. **a,** MHCII expression in HEK-293T cells was evaluated by immunofluorescent staining (red) at 48 hours post-transfection. Scale bar represents 30 μm. **b,** HEK-293T cells were desialylated using increasing concentrations of exogenous neuraminidase. At 24 hours post-treatment, α2,3 and α2,6 SA on the cell surface was examined by lectin binding and immunofluorescence. Scale bar represents 30 μm.

Supplementary Fig 3. Neuraminidase treatment completely removes sialic acid from HEK-293T cells after a 24-hour incubation.



Supplementary Fig 3. Neuraminidase treatment completely removes sialic acid from HEK-293T cells after a 24-hour incubation. HEK-293T cells were incubated for 24 hours at 37C with exogenous neuraminidase. After incubation, α2,6-SA **(a)** and α2,6-SA **(b)** levels on the cells surface were evaluated by lectin staining and flow cytometry. **c**, Median fluorescence intensity of samples treated and untreated with neuraminidase and a no lectin control determined by flow cytometry. **d.** Relative sialic acid levels on the cell surface were calculated by comparing the maximum fluorescence signal to non-treated HEK-293T cells (100%). Data are presented as the mean ± SEM of three independent experiments.

Supplementary Fig 4. Infection of desialylated cells lead to the infection of MHCII^{+} cells only.

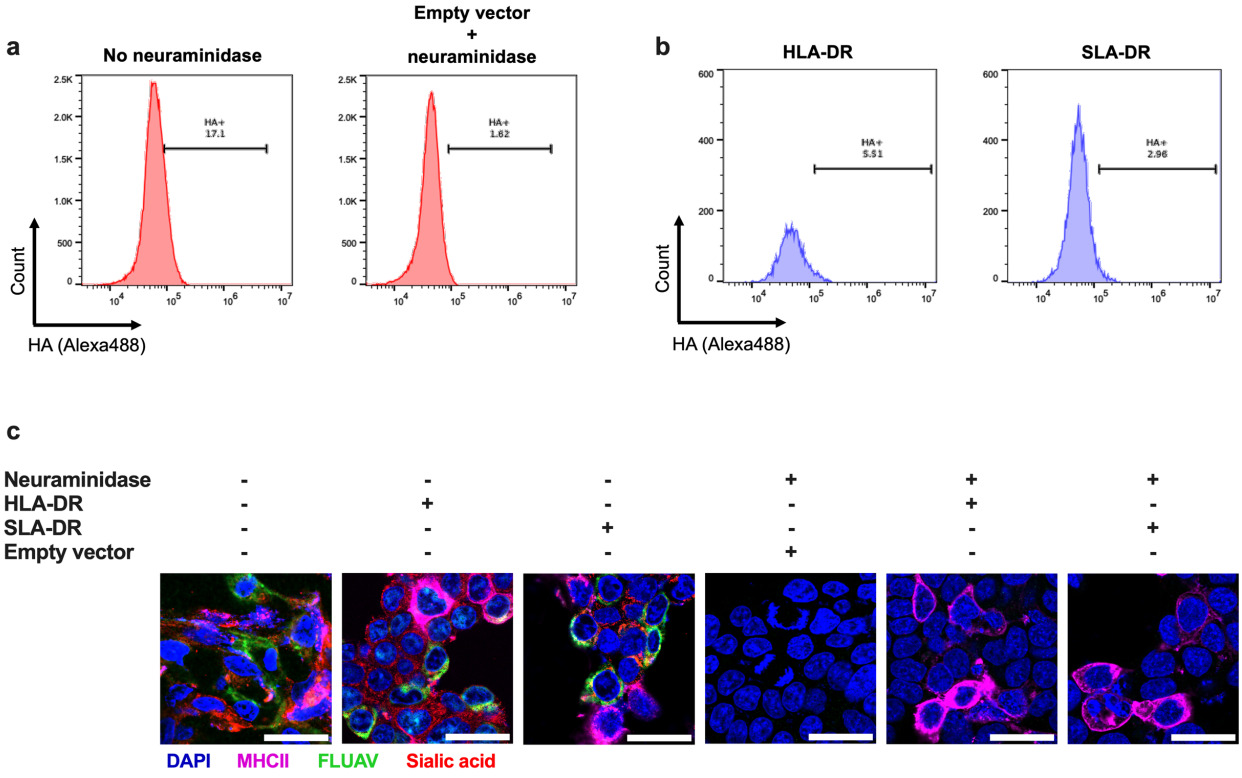


Supplementary Fig 4. Infection of desialylated cells lead to the infection of MHCII$^+$ cells only. a, Desialylated HEK-293T cells were transfected with MHCII-encoding plasmids and subsequently infected with either hVIC/11 (top panel) or sOH/04 (bottom panel) at 48 hours post-transfection. After a 24-hour incubation, cells were processed for flow cytometry and the percentage of infected cells among MHCII$^+$ and MHCII$^-$ cells was determined. **b,** Desialylated and non-desialylated HEK-293T cells were infected with either hVIC/11 (top panel) or sOH/04 (bottom panel). At 24 hpi, cells were processed for flow cytometry and the percentage of FLUAV-positive cells was determined for each condition. **c,** Non-desialylated HEK-293T cells were transfected with equimolar quantities of either HLA-DRA+HLA-DRB1 or SLA-DRA+SLA-DRB1. At 48 hpi cells were infected with either hVIC/11 (top panel) or sOH/04 (bottom panel) and the percentage of FLUAV-infected cells among MHCII$^+$ and MHCII$^-$ cells was determined by flow cytometry. Images are representative data of n=3 independent experiments.

Supplementary Fig 5. Protein sequence alignment of HLA-DR and SLA-DR alpha and beta subunits.

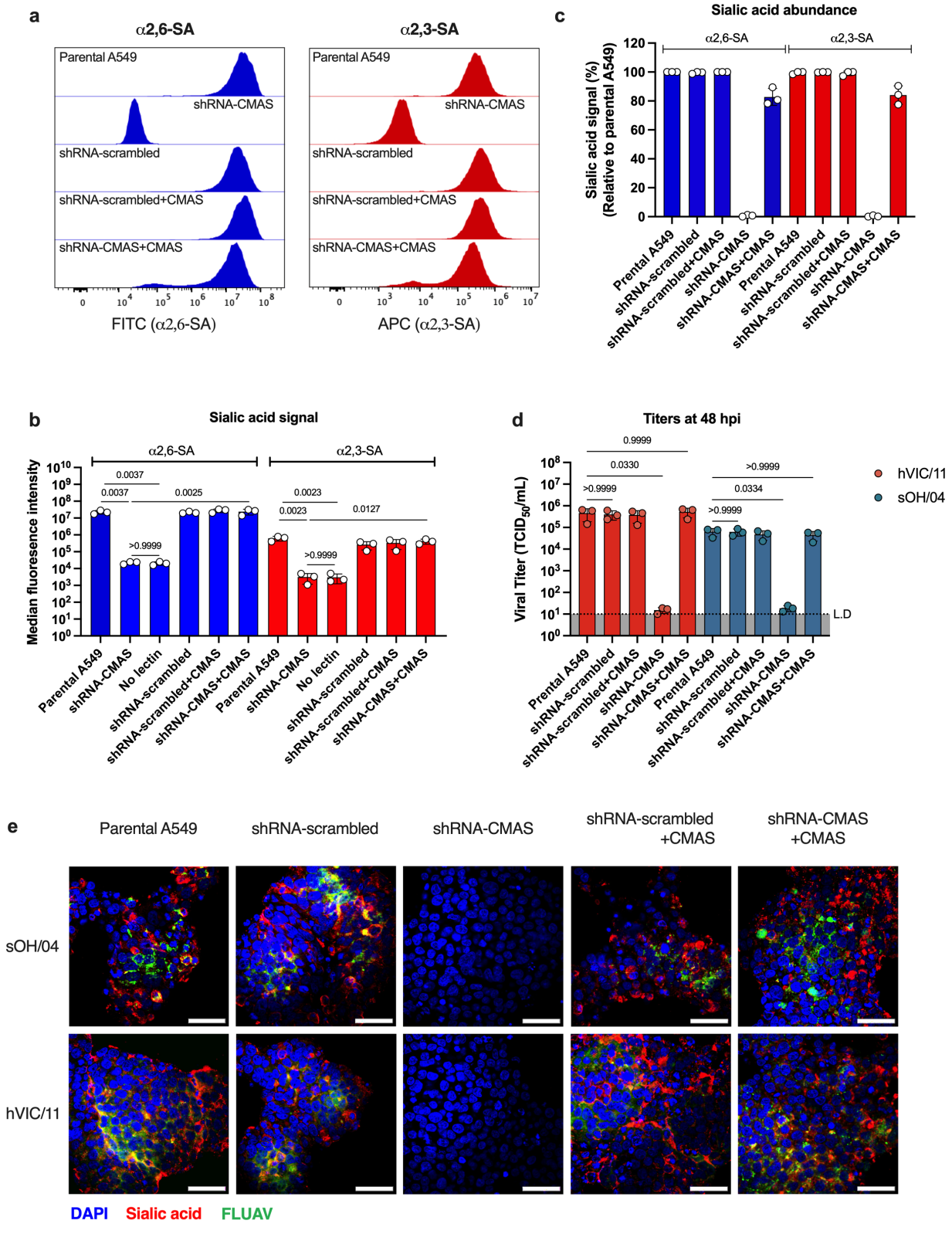
Supplementary Fig 5. Protein sequence alignment of HLA-DR and SLA-DR alpha and beta subunits. a, sequence alignment between HLA-DRA and SLA-DRA. Conserved amino acids are sown in red. **b,** Sequence alignment between HLA-DRB1 and SLA-DRB1. Conserved amino acid are highlighted in red.

Supplementary Fig 6. The pandemic 2009 H1N1 virus cannot infect desialylated MHCII^{+} cells.



Supplementary Fig 6. The pandemic 2009 H1N1 virus does not infect desialylated MHCII^{+} cells. a, Desialylated and non-desialylated HEK-293T cells were infected with the H1N1 virus and the percentage of infected cells was quantified at 24 hpi by flow cytometry. **b,** Desialylated HEK-293T cells were transfected with MHCII-encoding plasmids and subsequently infected with the pandemic H1N1 virus at 48 hours post-transfection. At 24 hpi post-infection, cells were harvested and stained for FLUAV and MHCII to determine the percentage of H1N1-infected cells by flow cytometry. **c,** HEK-293T cells were infected with the pandemic H1N1 virus and at 24 hpi cells were processed for immunofluorescence in which SA (red), MHCII (pink), and FLUAV (green) were stained. Scale bar represents 30 μm.

Supplementary Fig 7. CMAS silencing prevents sialic acid presentation on the cells surface and abolishes FLUAV infection.

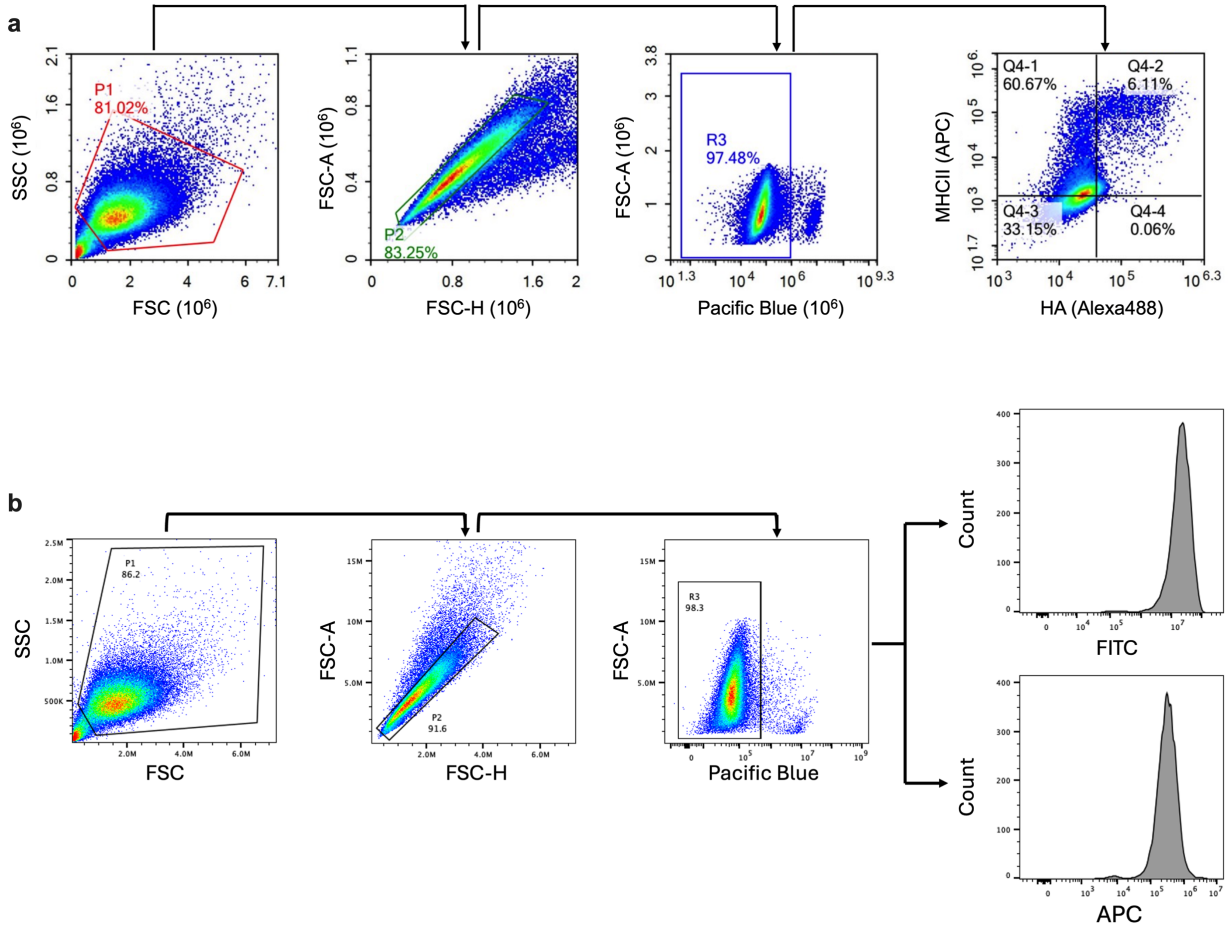


Supplementary Fig 7. CMAS silencing prevents sialic acid presentation on the cells surface and abolishes FLUAV infection. a, Sialic acid levels on the cells surface of parental A549 cells, A549 cells transduced with shRNA-CMAS, A549 cells transduced with shRNA-scrambled, or cells transduced with either shRNA-CMAS or scrambled reconstituted with a shRNA-resistant CMAS cDNA were evaluated by flow cytometry. **b.** Median fluorescence intensity of sialic acid from A549 cells described in **a** determined by flow cytometry. **c.** Relative sialic acid levels on the cell surface were calculated by comparing the maximum fluorescence signal to parental A549 cells (100%). **d**, cells described in **a** were infected with either sOH/04 or hVIC/11 at a MOI of 0.1. At 24 hpi, supernatants were collected at 24 hpi and viral titers under each condition were determined by RT-qPCR. **e.** Cells infected in **d** were harvested and stained for FLUAV (green) and sialic acid (red) for immunofluorescence. Scale bar represents 50 μm.

Supplementary Fig 8. Alignment between hVIC/11 and sOH/04 HA protein sequence.

Supplementary Fig 8. Alignment between hVIC/11 and sOH/04 HA protein sequence. Full length HA protein sequence alignment between hVIC/11 and sOH/04.

Supplementary Fig 9. Gating strategy used for MHCII, FLUAV-infected cells, and sialic acid detection.



Supplementary Fig 9. Gating strategy used for MHCII, FLUAV-infected cells, and sialic acid detection. Example of the gating strategy used in flow cytometry experiments. **a.** Gating strategy used to identify FLUAV-infected cells shown in Figures 2 and 4. **b.** Gating strategy used to determine sialic acid abundance on the cell surface in Figure 3.